

October 26, 2007

Nancy Sandrof
Manager, FND Panel
Fatty Nitrogen Derivatives Panel
Amines Task Group
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

Dear Ms. Sandrof:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Fatty Nitrogen Derived Ether Amines Category posted on the ChemRTK HPV Challenge Program Web site on March 25, 2004. I commend The American Chemistry Council's FND Panel Amines Task Group for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Amines Task Group advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsc hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Mark W. Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
R. Lee
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Fatty Nitrogen-Derived (FND) Ether Amines Category

Summary of EPA Comments

The sponsor, the American Chemistry Council's Fatty Nitrogen Derivatives (FND) Panel Amines Task Group, submitted a test plan and robust summaries to EPA for the FND Amines category dated December 23, 2002. In a letter dated July 10, 2003, the submitter informed EPA that the original submission posted on the ChemRTK HPV Challenge Web site on January 23, 2003 would be split into two separate submissions, an Ether Amines Category and an Amines Category. The Ether Amines Category test plan was submitted to EPA on December 29, 2003 and posted on the ChemRTK HPV Challenge Web site on March 25, 2004. The category consists of 6 sponsored FND ether amines. The submission also included information on 24 supporting chemicals (two FND ether amines and 22 FND amines).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Definition. The category definition is clear.
2. Category Justification. Structural features and measured and estimated physicochemical data support grouping the FND ether amines as a category.
3. Analog Justification. On the basis of physicochemical properties and aquatic toxicity data, the analogs appear reasonable for ecological effects. However, the rationale for using analog data for the health effects endpoints is inadequate; more specific discussion and explanation are needed. The proposed FND amine analogs are not appropriate for the biodegradation endpoint.
4. Physical Chemical Properties. The submitter needs to provide values and corresponding robust summaries for all six category members.
5. Environmental Fate. The submitter needs to provide modeled photodegradation and fugacity values for all six category members and measured ready biodegradation data for three of the category members.
6. Health Effects. To justify the use of analog data, the submitter needs to provide a thorough discussion of how the various data will be used to characterize the category members. The submitter also needs to consider testing for the repeated-dose, genetic toxicity (chromosomal aberrations) and reproductive/ developmental toxicity endpoints for at least one FND ether amine to better support hazard characterization and use of analog data.
7. Ecological Effects. Adequate data were submitted for all endpoints for the purposes of the HPV Challenge Program. Robust summaries need enhancement.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA Comments on The Fatty Nitrogen-Derived Ether Amines Category Challenge Submission

Category Definition

The submitter proposes a category of six sponsored FND ether amines: four long-chain substituted propanamines and two long-chain substituted propanediamines:

CAS No.	Sponsored Substance
68784-38-3	3-(C8-10-Alkyloxy) derivatives of 1-propanamine
30113-45-2	3-(Isodecyloxy)-1-propanamine
218141-16-3	3-(C9-11-Isoalkyloxy) derivatives of 1-propanamine, C10 rich

151789-06-9	3-(C11-14-Isoalkyloxy) derivatives of 1-propanamine, C13 rich
68479-04-9	N-[3-(Tridecyloxy)propyl]-1,3-propanediamine, branched
151789-07-0	N-(3-C11-14-Isoalkyloxy)propyl) derivatives of 1,3-

propanediamine, C13 rich

Additionally, 24 chemicals (two FND ether amines and 22 FND amines) were included as supporting chemicals in the submission. The 22 supporting FND amines are primary, secondary, and tertiary alkylamines ranging in chain length from C12 to C18, whereas the FND ether amines are all primary amines and contain an ether function. Two of the supporting FND amines contain C-terminal hydroxyl groups. The two supporting FND ether amines are the first two entries listed below.

CAS No.	Supporting Substance
28701-67-9	1-Propanamine, 3-(isodecyloxy)-, acetate
68511-40-0	1-Propanamine, 3-(tridecyloxy)-, branched
124-22-1	Dodecylamine
112-18-5	1-Dodecanamine, N,N-dimethyl
112-75-4	1-Tetradecanamine, N,N-dimethyl
143-27-1	Hexadecylamine
112-69-6	1-Hexadecanamine, N,N-dimethyl
3151-59-5 + 36505-83-6	Hexadecylamine hydrofluoride (Hetaflur) + 9-
Octadecen-1-amine	hydrofluoride
124-30-1	Octadecylamine
112-90-3	Cis-9-Octadecenylamine
4088-22-6	1-Octadecanamine, N-methyl-N-octadecyl
124-28-7	1-Octadecanamine, N,N-dimethyl
61788-46-3	Amines, coco alkyl
61788-93-0	Amines, coco alkyl dimethyl
61788-62-3	Amines, dicoco alkylmethyl
61791-31-9	Ethanol, 2,2'-iminobis-, N-coco alkyl derivs.
61788-45-2	Amines, hydrogenated tallow alkyl
61788-95-2	Amines, (hydrogenated tallow alkyl)dimethyl
61789-79-5	Amines, bis(hydrogenated tallow alkyl)
61788-63-4	Dihydrogenated tallow methylamine
61790-33-8	Amines, tallow alkyl
61791-55-7	Amines, N-tallow alkyltrimethylenedi-
61791-44-4	Ethanol, 2,2'-iminobis-,N-tallow alkyl derivs.
61788-91-8	Amines, dimethyl soya alkyl

Category Justification

The submitter's rationale for grouping the FND ether amines into a single category is based on the structural similarity of the chemicals and the surfactant properties associated with the structures as well as similarities in their environmental fate and toxicity. The submitter uses measured and estimated/modeled data for 22 supporting FND amines and two non-sponsored FND ether amines for non-health endpoints to support the category.

The submitter's category justification is cursory and too generalized, lacking specific examples. Although not specifically stated in the test plan, the basis for the submitter's approach appears to be (1) that the 22 FND amines have a similar and consistent set of test data; (2) that the estimated values (for non-health endpoints) for the 22 FND amines are consistent with the measured data (so that predictive methods are valid for use within this structural class); (3) that the estimated values (for non-health endpoints) for the FND ether amine category members are similar to the estimated values and test data available for the 22 FND amines (so that measurements and estimates made for the 22 FND amines will be representative of the category members); and (4) that the available test data for the two FND ether

amine analogs are consistent with the other available information.

Physical chemical properties. The submitted data for FND ether amines appear consistent across the category and are similar to the data for the FND amines. Measured and estimated values are consistent with the size of the alkyl groups across both the FND amines and FND ether amines. No readily discernable pattern was seen for structural types among the FND amines (e.g., primary vs. tertiary amines), although the properties appear to be dominated more by the hydrophobic structures within each molecule than the hydrophilic portions.

Environmental fate. Predicted values for photodegradation and transport and distribution of the FND ether amines follow a pattern based on molecular size. Although similar measured biodegradation rates were reported for CAS Nos. 30113-45-2 (category member) and 20701-67-9 (supporting ether amine), this is expected and redundant since the latter is merely a salt of the former.

Health effects. No data are available for the sponsored substances. Similar acute oral rodent LD50 values and negative results of Ames tests were reported for the supporting ether amines CAS Nos. 28701-67-9 and 68511-40-0 and the FND amines. These data suggest minimal variation in these effects with structure and appear to support these two endpoints for the FND ether amines category. However, no adequate data are available for FND ether amines for the chromosomal aberrations, repeated-dose, reproductive, or developmental toxicity endpoints to provide additional category support.

Ecological effects. For CAS No. 68479-04-9, experimental values of less than 1 mg/L were reported for the 96-hour LC50 for freshwater fish and the 48-hour EC50 for daphnia. These values are consistent with the toxicity values reported for fish and daphnia for the FND amines, suggest minimal variation of toxicity with variation in structure, and support treating the FND ether amines as a category.

EPA concludes that the six sponsored FND ether amines span a relatively narrow structural range of primary amines and, although the two types of ether amines are distinct (mono- and dipropanamines), they are sufficiently similar that their grouping into a single category is reasonable on a structural basis. Measured and estimated data for physicochemical properties also lend support to the category. The final category analysis will need to specifically and critically address the structural variations (mono- vs. diamines, branched vs. straight-chain alkyl groups, alkyl chain length, mixture issues, etc.)

Analog Justification

The submitter uses measured and estimated/modeled data for 22 supporting FND amines and two non-sponsored FND ether amines for non-health endpoints to support a read-across approach for most of the SIDS endpoints.

The two non-sponsored FND ether amines are structurally similar to the category members (one is simply a salt of a category member) and hence are reasonable analogs. However, the 22 supporting FND amines span a much larger range of structures and molecular weights than the FND ether amines, do not form a single structural category, and differ from the FND ether amines in having no ether function and apparently no chain branching; some have unsaturation and di- or trialkyl substitution on nitrogen, and most have longer chain lengths. Thus, it is anticipated that the FND ether amines will have relatively higher water solubility values, lower octanol/water partition coefficients, and greater surfactant properties than 20 of the 22 FND amine analogs since the presence of the ether function adds to the polar character of the hydrophilic portion of the molecule (two of the FND amines contain hydroxyl groups and are expected to have properties that reflect these hydrophilic groups). These expected ether function-mediated differences in physicochemical properties, together with the lack of chain branching among the FND amines, suggest that the FND amines will not adequately represent the behavior of the FND ether amines for some SIDS endpoints for the purposes of the HPV Challenge Program. However, for the ecological effects endpoints, although there is a range of toxicity values, the differences appear related to the test methodology, especially for those studies that suggest lower toxicity, or where testing was done

above the water solubility limit. Missing key data elements such as total organic carbon, water hardness, pH, and temperature that will impact the toxicity values significantly should be provided, if available. Nonetheless, the submitted data on several substances are adequate to characterize the aquatic toxicity of the FND ether amines for the purposes of the HPV Challenge Program.

The FND ether amines and supporting substances have varying chain lengths and (for the FND amines) degrees of unsaturation that likely have no significant impact on the aquatic toxicity and most of the environmental fate endpoints. However, none of the supporting FND amines appear to be branched, so that the FND amine data are inappropriate to characterize biodegradation for five of the six ether amines (biodegradation rates are sensitive to chain branching). Moreover, the only available ether amine data show a lack of ready biodegradability, whereas the FND amines are often, but not consistently, readily biodegradable.

For health effects the submitter did not provide any repeated-dose, genetic (chromosomal aberrations) or reproductive/developmental toxicity data for any of the category members, and the Test Plan does not describe in specific terms just how the supporting chemical data will be used to characterize the sponsored substances. Furthermore, no such data were provided for the sole diamine among the FND amines. To justify the use of the analog data, the submitter needs to provide at minimum a thorough discussion, citing specific data on specific substances, of how the data can be used to characterize the ether amines category; the reader should not have to draw conclusions from data scattered throughout the tables. The final category analysis will need to specifically and critically address the structural variations (mono- vs. diamines, branched vs. straight-chain alkyl groups, alkyl chain length, mixture issues, olefin content, etc.).

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The submitter needs to provide all data for the six sponsored substances in robust summary format. Data in tabulated format in the test plan are inadequate for the purposes of the HPV Challenge Program. Where estimations are appropriate for the mixtures, the submitter needs to use representative structures.

The table 5 footnotes cite "R=Read across from available data and/or experimental determination is considered inappropriate"; it seems more likely that the submitter intended to say "...is considered appropriate". However, EPA does not agree with a read-across approach for these endpoints. A measured or modeled value is needed for each category member for each endpoint.

Melting point. The data provided by the submitter are inadequate for the purposes of the HPV Challenge Program. The submitter provided estimated melting point values for CAS No. 30113-45-2 (51 oC) and CAS No. 68479-04-9 (81 oC). In general, estimated melting point values are not adequate for the purposes of the HPV Challenge Program; values above 0 oC need to be measured. The submitter needs to provide melting point values (or decomposition or softening points as appropriate) for all six category members.

Boiling point. The estimated boiling point value provided for CAS No. 30113-45-2 (278 oC) is inadequate for the purposes of the HPV Challenge Program; values under 300 oC need to be measured. The submitter needs to provide boiling point (or decomposition) values for all six category members.

Vapor pressure. The data provided by the submitter are inadequate. The submitter provided estimated vapor pressure values for CAS No. 30113-45-2 (3.5×10^{-3} hPa) and CAS No. 68479-04-9 (2.2×10^{-6} hPa). The submitter needs to provide vapor pressure values for all six category members; values above

1 x 10⁻⁷ hPa need to be measured.

Octanol/water partition coefficient. Estimated partition coefficient values are adequate for these substances for the purposes of the HPV Challenge Program. However, they cannot be used to predict values for other category members. The submitter needs to provide partition coefficient data for all category members.

Water solubility. The data provided by the submitter are inadequate. The submitter provided estimated water solubility values for CAS No. 30113-45-2 (165 mg/L), and CAS No. 68479-04-9 (2.64 mg/L). The submitter also reports that water solubility measurements of surfactants can be difficult because these chemicals can form micelles and suspensions in aqueous systems. This may only be an issue for the two propanediamines within this category as the monoamines are not expected to have strong surfactant properties. The submitter needs to provide water solubility values for all six category members; values above 1 µg/L need to be measured.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Photodegradation. Estimated photodegradation values are adequate for the purpose of the HPV Challenge Program. However, they cannot be used to predict values for the remaining members. The submitter needs to provide photodegradation data for the other four category members.

Stability in water. EPA agrees that the chemicals in this category do not have hydrolyzable groups. However, in table 6 of the test plan, the submitter indicates that the data for CAS No. 30113-45-2 and CAS No. 68479-04-9 will be used to characterize the other four chemicals in this category. EPA disagrees with this approach. The submitter needs to delete that language and state in the robust summary for each chemical that it does not have hydrolyzable functions.

Biodegradation. The data provided by the submitter are inadequate. The submitter indicates in table 6 of the test plan that it will use the data for CAS Nos. 30113-45-2 and 28701-67-9 (ether amine analog – the acetate salt of CAS Nos. 30113-45-2) to characterize the monoamine category members and use data for an alkyl diamine (CAS No. 61791-55-7) to characterize the two propanediamine mixtures within this category, and asserts that additional testing is not required. EPA disagrees with this approach. First, the data provided in support of the two propanediamine mixtures are from an inherent test (Zahn-Wellens test) and are not suitable for the evaluation of this endpoint. Second, to adequately characterize the six category members, the submitter needs to provide measured ready biodegradation data for the linear substance CAS No. 68784-38-3 and the branched diamines CAS No. 68479-04-9 (more branching) and CAS No. 151789-07-0 (less branching). The submitter then may use the data set to characterize the other category members.

The submitter needs to provide a complete robust summary for each study cited. Submitting data only in test plan tables is inadequate for purposes of the HPV Challenge Program.

The test plan states that CAS No. 30113-45-2 is “inherently degradable” in an OECD 301B test (45% degradation in 28 days). Stating that a chemical is inherently biodegradable in a test for ready biodegradation may not be accurate. The submitter needs to state that this result shows the chemical is “not readily biodegradable.”

Fugacity. Estimated fugacity values are adequate for the purpose of the HPV Challenge Program. However, they cannot be used to predict fugacity values for other category members. The submitter needs to provide fugacity data for the other four category members using measured input values for each chemical where possible. EPA agrees with the submitter’s assumption that because releases are mainly to wastewater treatment plants, release to the environment would be completely to water.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Acute toxicity data submitted for CAS No. 28701 67 9 and gene mutation data for CAS No. 68511-40-0, supported by corresponding data on FND amines, were adequate to characterize the category for these two endpoints for the purposes of the HPV Challenge Program. The submitter needs to provide the robust summary for the Ames study claimed for CAS No. 28701-67-9.

As explained in the Analog Justification section, in order to justify the use of the analog data for the remaining endpoints, the submitter needs to provide at minimum a thorough discussion, citing specific data on specific substances, of how the data on such structurally diversified analogs can be used to characterize the ether amines category. Ideally, the submitter should develop data according to OECD TG 422 (combined repeated-dose/reproductive/developmental study) and OECD TG 473 (in vitro chromosomal aberrations) for at least one FND ether amine to provide adequate analog justification.

Ecological Effects (fish, invertebrates, and algae)

The available measured and estimated data indicate that the FND ether amines are highly toxic to aquatic organisms. The submitter stated that further testing is unwarranted because it would not provide any new information about the toxicity of these chemicals, and that for the purposes of the HPV Challenge program, all of the FND Ether Amine Category chemicals should be considered highly toxic to aquatic organisms. This approach is reasonable. However, the submitter should provide, if available, the data elements missing from the robust summaries to allow for an independent evaluation of the data and help explain certain test results. In particular, the total organic carbon (TOC) content can help determine how much of the toxicity has been mitigated by test chemical binding to organic carbon in test water. Also, the submitter needs to be aware that the log Kow cut-off with the ECOSAR model for amine toxicity predictions is 7.0.

Specific Comments on the Robust Summaries

Physicochemical Properties and Environmental Fate

The submitter needs to provide robust summaries for each endpoint for each chemical. It is not adequate only to present tabulated data in the test plan.

Health Effects

Acute toxicity. If available, the test substance purity should be included in the robust summary.

Genetic toxicity (Gene mutations). If available, these study details should be included: statistical methods used, test substance purity, the source of the metabolic activation system, mean number of revertant colonies per plate, and the criteria for evaluating results.

Ecological Effects

Fish, Invertebrates, Algae. Where applicable all robust summaries for the key studies should provide total organic carbon (TOC), pH, water hardness, water temperature, and chemical purity, and indicate whether the chemical has been neutralized to pH 7.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.